



Nucleophilic Addition to Carbonyl: Grignard Reaction with an Aldehyde

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PURPOSE OF THE EXPERIMENT

Demonstrate formation of a carbon–carbon bond using the addition of a Grignard reagent across the carbonyl of an aldehyde. Characterize the product using thin-layer chromatography, infrared spectroscopy, and nuclear magnetic resonance spectroscopy.

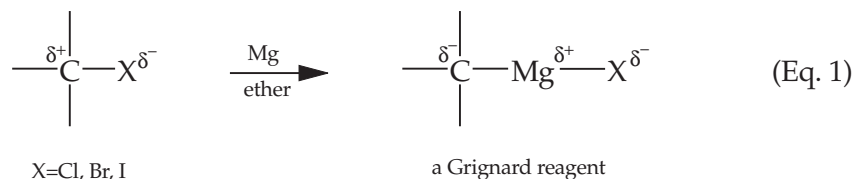
BACKGROUND REQUIRED

You should be familiar with using a Bunsen burner, packing a drying tube, and drying organic layers. You should also be familiar with techniques for magnetic stirring, reflux, distillation, extraction, solvent evaporation, thin-layer chromatography, infrared spectroscopy, and nuclear magnetic resonance spectroscopy.

BACKGROUND INFORMATION

Victor Grignard began his investigations into the reaction of organic halides with magnesium at the turn of the twentieth century. For this work, he received the 1912 Nobel Prize in Chemistry. In the history of organic chemistry, no other reaction has had greater significance than the Grignard reaction for its scope, simplicity, and versatility.

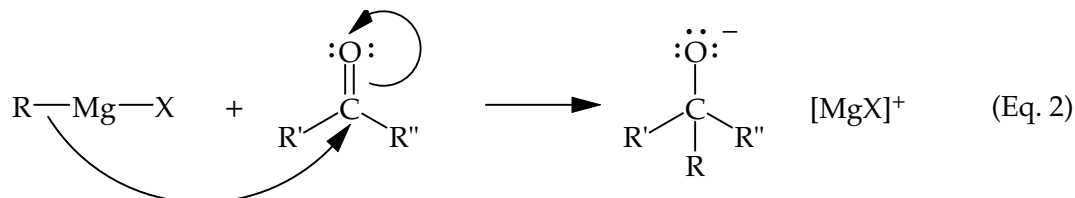
Common nonmetals such as oxygen, nitrogen, and the halogens are more electronegative than carbon. As a result, a carbon bonded to these atoms has a partial positive character. When magnesium is inserted between the carbon and a halogen, however, the polarity is reversed because carbon is more electronegative than magnesium. This process transforms carbon from an electrophilic atom to a nucleophilic one, as shown in Equation 1. The Grignard reaction was the first reaction to generalize the use of carbon as a nucleophile to make carbon–carbon bonds.



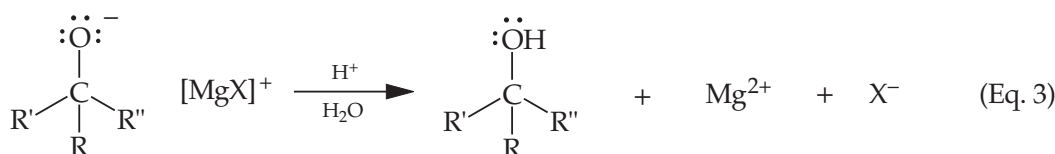
The structure of a Grignard reagent in solution has been the subject of much study. In fact, a Grignard reagent cannot be isolated without a solvent present. The nonbonded electrons from the oxygen in an ether

solvent or the nitrogen in an amine solvent are necessary to stabilize a Grignard reagent. The standard way of indicating a Grignard reagent, RMgX , is not an accurate representation of the larger aggregate in solution. The stoichiometry works, however, as if RMgX were the actual reactive species. For simplicity, chemists continue to use this designation.

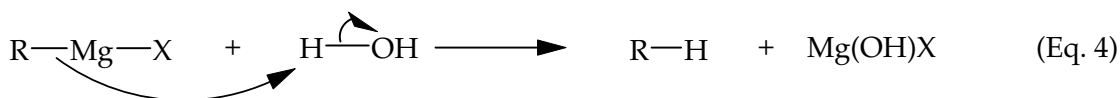
The nucleophilic carbon of a Grignard reagent rapidly adds to the carbonyl carbon of an aldehyde or ketone, as shown in Equation 2. A Grignard reagent can also react with esters, acid chlorides, nitriles, epoxides, and carbon dioxide.



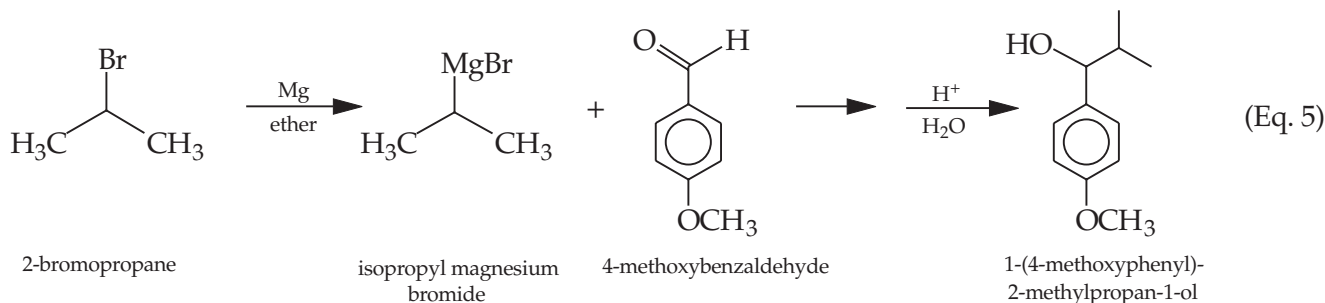
Hydrolysis of the resulting complex with aqueous acid produces an alcohol, as shown in Equation 3. The reaction of a Grignard reagent with formaldehyde produces a primary alcohol. With any other aldehyde, the Grignard reaction produces a secondary alcohol. With a ketone, the Grignard reaction produces a tertiary alcohol.



The greatest practical challenge in preparing a Grignard reagent is to keep water out of the reaction. The negative charge of the carbon in the Grignard reagent makes the carbon very basic. Water can donate a proton to the carbon, destroying the nucleophilic character of the Grignard reagent, as shown in Equation 4. Several precautions are taken in the procedure to exclude water: the reaction flask is flame-dried before adding solvent; a drying tube keeps moisture from entering the apparatus; iodine is vaporized in the flask to tie up traces of water and to activate the surface of the magnesium; the diethyl ether solvent is specially dried and packaged to guarantee that it is anhydrous.



In this experiment, you will prepare the Grignard reagent isopropylmagnesium bromide from 2-bromopropane. You will react this Grignard reagent with 4-methoxybenzaldehyde to form a secondary alcohol, 1-(4-methoxyphenyl)-2-methylpropan-1-ol, as shown in Equation 5.



Equipment

50-mL beaker	magnetic stir bar
100-mL beaker	magnetic stirrer
250-mL beaker*	magnetic wand [‡]
boiling chip	microspatula
Bunsen burner	paper towel
capillary tubes [†]	Pasteur pipet, with latex bulb
condenser, with tubing	pencil
cotton	pH paper
distilling head	1.0-mL pipet
drying tube, with stopper	product vial
2 Erlenmeyer flasks, 25-mL	2 round-bottom flasks, 50-mL
2 Erlenmeyer flasks, 50-mL, with stopper	ruler
250-mL Erlenmeyer flask	125-mL separatory funnel
filter funnel	3 × 7-cm silica gel TLC plate
fluted filter paper	2 support stands
25-mL graduated cylinder	2 utility clamps
4-oz jar, with lid [§]	2.0-mL vial, with cap

*or concentric ring bath for hot-water bath

[†]for preparing micropipets

[‡]or glass stirring rod

[§]or 250-mL beaker with foil or plastic wrap as cover for TLC developing chamber

Reagents and Properties

<i>substance</i>	<i>quantity</i>	<i>molar mass</i> (g/mol)	<i>mp</i> (°C)	<i>bp</i> (°C)
2-bromopropane	1.48 g	123.0		59
calcium chloride, anhydrous	8 g*	110.99		
dichloromethane	5 mL	84.93		40
diethyl ether, anhydrous	20 mL	74.12		34.6
diethyl ether, solvent grade	22 mL	74.12		34.6
iodine	0.02 g	253.8	113	184
magnesium	0.36 g	24.3		
magnesium sulfate, anhydrous	2 g	120.37		
4-methoxybenzaldehyde	0.68 g	136.15	-1	248
1-(4-methoxyphenyl)- 2-methylpropan-1-ol [†]		180.21		
phosphoric acid, 1M	15 mL			
sodium chloride, saturated solution	10 mL			
sodium hydroxide, 5%	10 mL			

*amount varies, depending on size of drying tube

[†]product

Preview

- Assemble the reflux apparatus
- Flame-dry a round-bottom flask

- Weigh magnesium turnings
- Add magnesium and iodine to the dried round-bottom flask
- Heat the reflux apparatus to flood the apparatus with iodine vapor
- Weigh 2-bromopropane and dissolve it in *anhydrous* diethyl ether
- Add 2-bromopropane solution to the magnesium turnings and reflux to make the Grignard reagent
- Weigh 4-methoxybenzaldehyde and dissolve it in *anhydrous* diethyl ether
- Add 4-methoxybenzaldehyde portions to the Grignard reagent
- Heat 10 min with a hot-water bath
- Pour the mixture into ice water and acidify it with phosphoric acid
- Separate the layers
- Extract the product into ether and wash it with 5% NaOH and saturated NaCl solution
- Dry the ether layer with anhydrous magnesium sulfate
- Remove the ether from the product
- Weigh the product
- Characterize the product using TLC, IR, and NMR

PROCEDURE *Chemical Alert*

2-bromopropane—*flammable and irritant*
 calcium chloride—*irritant and hygroscopic*
 dichloromethane—*toxic and irritant*
 diethyl ether—*flammable and toxic*
 iodine—*toxic and corrosive*
 magnesium—*flammable*
 4-methoxybenzaldehyde—*irritant*
 phosphoric acid—*corrosive*
 5% sodium hydroxide—*toxic and corrosive*

Caution: Wear departmentally approved safety goggles at all times while in the chemistry laboratory.

1. **Drying the Apparatus** **Caution:** Iodine (I₂) is toxic and corrosive. Magnesium (Mg) is flammable. Keep away from flames or other heat sources. Calcium chloride (CaCl₂) is irritating and hygroscopic. Prevent eye, skin, and clothing contact. Avoid inhaling and ingesting these compounds. Use a *fume hood*.

Place two 25-mL Erlenmeyer flasks in a drying oven. Pack a drying tube with anhydrous CaCl₂.

Clamp a dry 50-mL round-bottom flask to a support stand. Add a magnetic stir bar. Using a medium flame from a Bunsen burner, flame (heat) all outer surfaces of the flask, starting at the bottom and working up until no more water vapor condenses on the flask.

Insert the drying tube into the neck of the flask and cool the flask for 5 min. Remove the drying tube.

Weigh 0.36 g of Mg turnings. Add the turnings and 3–4 crystals of I_2 to the flask.

Insert the dry condenser into the round-bottom flask. Place the drying tube in the top of the condenser.

Use the Bunsen burner flame to gently heat the round-bottom flask until I_2 vapor fills the flask. Allow the apparatus to cool to room temperature.

When the apparatus is cool, place a magnetic stirrer under the round-bottom flask of the apparatus, as shown in Figure 1. Attach tubing to the condenser and begin a slow flow of tap water through the condenser.

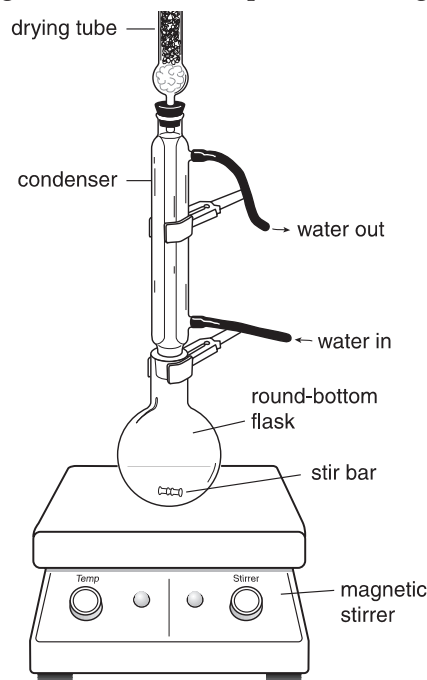


Figure 1 Reflux apparatus for the Grignard reaction

2. Preparing the Grignard Reagent

Caution: 2-Bromopropane is flammable and irritating. Diethyl ether is highly flammable and toxic. Do not use near flames or other heat sources. *Make certain all burners in the laboratory are extinguished before opening the container of diethyl ether.* Prevent eye, skin, and clothing contact. Avoid breathing fumes and ingesting these compounds. Use a *fume hood*.

NOTE 1: 2-Bromopropane is volatile. Product yield will be low if ether is not added immediately after weighing 2-bromopropane.

NOTE 2: The reaction should begin within 2 min and produce enough heat to boil the ether. If the reaction does not begin within 5 min, notify your laboratory instructor.

In a cool, *dry* 25-mL Erlenmeyer flask, weigh 1.48 g (1.13 mL) of 2-bromopropane. [NOTE 1] *Immediately* add approximately 10 mL of *anhydrous* diethyl ether by pouring directly from the ether container.

Remove the drying tube from the top of the reflux condenser. Pour the 2-bromopropane solution through the condenser into the round-bottom flask. [NOTE 2] When you observe rapid boiling, adjust the magnetic stirrer to slow or medium speed.

When the boiling begins to subside, prepare a hot-water bath by filling a 250-mL beaker with *hot* tap water. Place the bath under the round-bottom flask. Immerse the flask until the water level in the bath is even with the reaction mixture level in the flask.

Warm the flask for 10–15 min to complete the formation of the Grignard reagent. Remove the hot-water bath and allow the solution to cool to room temperature.

3. Reacting the Grignard Reagent and the Aldehyde

Caution: 4-Methoxybenzaldehyde is irritating. Prevent contact with eyes, skin, and clothing. Avoid breathing fumes and ingesting the compound.

Weigh 0.68 g of 4-methoxybenzaldehyde (*p*-anisaldehyde) into a cool, dry 25-mL Erlenmeyer flask. Add approximately 10 mL of *anhydrous* diethyl ether by pouring from the container.

Remove the drying tube from the top of the reflux condenser. Over 5–10 min, use a Pasteur pipet to add the 4-methoxybenzaldehyde solution in approximately 0.5-mL portions through the condenser into the round-bottom flask. Replace the drying tube after each addition. Add the solution at such a rate that the stirred reaction mixture refluxes gently.

After all of the solution is added, warm the stirred reaction mixture with a hot-water bath for 10 min. Then allow the reaction mixture to cool to room temperature.

4. Isolating the Product

Caution: Phosphoric acid (H_3PO_4) is corrosive. Sodium hydroxide (NaOH) is toxic and corrosive. Prevent contact with eyes, skin, and clothing. Avoid breathing fumes and ingesting the compounds.

Prepare an ice-water mixture by filling a 250-mL Erlenmeyer flask with ice to the 50-mL mark. Add distilled or deionized water to the 50-mL mark.

Set the Erlenmeyer flask containing the ice water on the magnetic stirrer. Add a stir bar. [NOTE 3] Adjust the stirrer to a rapid rate.

Remove the round-bottom flask from the apparatus. Then gradually pour the reaction mixture into the ice water.

Rinse the round-bottom flask with 4–5 mL of 1M H_3PO_4 and add the rinse to the reaction mixture in the ice water. Rinse the round-bottom flask with 10 mL of solvent grade diethyl ether. Add this rinse to the reaction mixture.

Continue to stir the mixture rapidly. Gradually add enough 1M H_3PO_4 until the mixture is acid to pH paper.

Place a filter funnel in the top of a 125-mL separatory funnel. Place a *loose* piece of cotton in the filter funnel. Pour the mixture through the cotton into the separatory funnel. Then remove the filter funnel.

Allow the layers to separate. Drain the aqueous layer from the separatory funnel into a 100-mL beaker. Pour the ether layer into a 50-mL Erlenmeyer flask and stopper the flask.

Return the aqueous layer to the empty separatory funnel and extract with a second 10-mL portion of ether. Again drain the aqueous layer into the beaker. Pour the aqueous layer into the container labeled “Acidic Aqueous Layer”, provided by your laboratory instructor. Rinse the beaker with water.

Add the original ether solution to the second ether layer in the separatory funnel. Wash the combined ether layer with 10 mL of 5% aqueous NaOH . Drain the NaOH layer into the 100-mL beaker. Pour the NaOH layer into the container labeled “Recovered 5% NaOH ”, provided by your laboratory instructor. Rinse the beaker with water.

NOTE 3: Use a magnetic wand to transfer the stir bar from the round-bottom flask to the Erlenmeyer flask.

NOTE 4: Add anhydrous MgSO_4 to the solution gradually until the solution is no longer cloudy or until the MgSO_4 no longer clumps. Approximately 2 g will be required.

Wash the ether layer with 10 mL of saturated NaCl solution. Drain off the aqueous layer into the 100-mL beaker.

Transfer the ether solution to a dry 50-mL Erlenmeyer flask. Add enough anhydrous magnesium sulfate (MgSO_4) to dry the solution. [NOTE 4] Stopper the flask and allow the solution to dry for 5 min. Then filter the solution through a fluted filter paper into a *tared* 50-mL round-bottom flask.

5. Removing the Ether

[NOTE 5]

NOTE 5: Use the separation method designated by your laboratory instructor.

Using a Rotary Evaporator

Use a rotary evaporator to collect the ether from the product, as directed by your laboratory instructor. Weigh the round-bottom flask containing your liquid product and record the mass. Place your product in a product vial labeled "Grignard Product".

Using Distillation

Set up a simple distillation apparatus in the *fume hood*. Use the 50-mL round-bottom flask containing your product as the distilling flask. Add a boiling chip. Use a hot-water bath to distill the ether from the product. Collect the ether in a 50-mL beaker.

Allow the apparatus to cool. Remove the boiling chip. Weigh the round-bottom flask containing your liquid product and record the mass. Place your product in a product vial labeled "Grignard Product".

6. Characterizing the Product

Caution: Dichloromethane is toxic and irritating. Prevent eye, skin, and clothing contact. Avoid inhaling vapors and ingesting the compound. Use a *fume hood*.

Using TLC

Place 0.1 mL of your product into a 2.0-mL vial. Add 1.9 mL of anhydrous diethyl ether. Cap the vial to prevent evaporation.

Obtain a 3 × 7-cm silica gel thin-layer chromatography (TLC) plate from your laboratory instructor. Draw a *very faint* pencil line 1 cm from the bottom to mark the origin. Make two vertical marks that intersect the pencil line 0.5 cm from each edge of the plate and a third mark 1.5 cm from one edge.

Prepare micropipets for spotting the TLC plate by drawing out melting point capillary tubing. Using a micropipet, spot a standard sample of 4-methoxybenzaldehyde once on the middle mark, keeping the spot as small as possible. Using a new micropipet, spot your product–diethyl ether sample once on the left-hand mark. Using the same micropipet, spot your sample twice on the right hand mark, allowing the ether to evaporate between spottings.

Prepare a developing chamber by pouring 5 mL of dichloromethane into a 4-oz jar. Place the TLC plate into the chamber, making certain the origin is higher than the eluent. Attach the lid. Allow the eluent to develop the plate.

Caution: Ultraviolet radiation can cause severe eye damage. Wear goggles. Do not look directly into the UV lamp.

After developing the plate, mark the eluent front. Visualize the chromatogram under short-wave UV light. Use a pencil to circle the spots on your plate.

Using IR Spectroscopy

Obtain an IR spectrum of your sample. Identify the major peaks and compare your spectrum with a spectrum of 4-methoxybenzaldehyde, provided by your laboratory instructor.

Using NMR

Obtain an NMR spectrum of your sample. Compare your spectrum with a spectrum of 4-methoxybenzaldehyde, provided by your laboratory instructor.

7. **Cleaning Up** Use the labeled collection containers as directed by your laboratory instructor. Clean your glassware with soap or detergent.

Caution: Wash your hands with soap or detergent before leaving the laboratory.

Post-Laboratory Questions

1. Calculate the percent yield for your product.
2. What is the purpose of adding anhydrous MgSO_4 to the ether solution? What would occur if this step were omitted?
3. Calculate the R_f s for all spots on your chromatogram.
4. (a) Identify the spots in the TLC.
(b) Does TLC indicate the presence of any unreacted aldehyde?
(c) What does the TLC show about the polarity of the product compared with the polarity of the aldehyde?
5. What peak in the IR spectrum most clearly demonstrates the presence of alcohol product? If the product had unreacted aldehyde remaining, what IR peak would indicate the presence of this contaminant?
6. (a) What peaks in the NMR spectrum most clearly demonstrate the presence of the predicted product?
(b) If the product had unreacted aldehyde remaining, what NMR peak would indicate the presence of this contaminant?
7. Draw a Newman projection along C(1)–C(2), with the OH group attached to C(1). Are the two methyl groups equivalent? What evidence do you find from the NMR spectrum to support your conclusion?

NAME

SECTION

DATE

SYNT 718/Nucleophilic Addition to Carbonyl: Grignard Reaction with an Aldehyde

Pre-Laboratory Assignment

1. Describe the safety hazards for diethyl ether.
2. Write the chemical reactions for the formation of the respective Grignard reagents from the reaction of magnesium with the following organic halides:
 - (a) iodomethane
 - (b) bromobenzene
 - (c) chlorocyclohexane
3. Write the reactions of methylmagnesium iodide with the following aldehydes and ketones. Assume that all reactions include a hydrolysis in aqueous acid.
 - (a) formaldehyde (methanal), CH_2O
 - (b) acetone
 - (c) cyclohexanone

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4. (a) What is the common purpose of these precautions: flaming the apparatus before running the reaction; using a drying tube to separate the atmosphere inside the apparatus from the outside air; and using anhydrous ether as the solvent?

(b) What could be the undesired result if these precautions were not followed?
5. Why is the Grignard reagent prepared in excess relative to the aldehyde?
6. Show the reaction of excess Grignard reagent with aqueous acid.
7. Calculate the theoretical yield of the product, 1-(4-methoxyphenyl)-2-methylpropan-1-ol. Show your calculation here and in your laboratory notebook.
8. (a) When analyzing the product using TLC, why is it helpful to spot the reactant on the same plate as the product?

(b) Why not spot just the product?
9. Indicate the major differences between the IR spectra of the reactant aldehyde and the product alcohol.